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Towards a biomimetic synthesis of barrenazine A

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Abstract—We report herein a concise and biomimetic synthesis of a precursor of barrenazine A, a cytotoxic alkaloid. The C_2-symmetry of this molecule suggested the dimerization of an aminoketone, as the precursor of the central core pyrazine. This compound was prepared by assembly of aspartic acid and glycine.

1. Introduction

In 2003[1] was reported the structural assignment of two new cytotoxic alkaloids named barrenazines A and B, extracted from a tunicate collected at Barren Islands, Madagascar. These compounds display an interesting symmetrical structure, consisting of a central pyrazine ring, fused with two piperidines with a central C_2-symmetry. More recently,[2] an elegant synthesis involving a diastereoselective addition of a Grignard reagent onto a pyridinium salt was accomplished.

The presence of the pyrazine ring prompted us to synthesize the central core of this molecule via condensation of two identical aminoketones. Both stereogenic carbon centres exhibiting the same stereochemistry revealed two aspartic acid-derived synthons. Thus, we focused on a retrosynthesis based on the dimerization of the aminoketone resulting from C-acylation of glycine by aspartic acid side-chain carbonyl as shown in Scheme 1.

The stereochemistry of the target molecule is consistent with that of natural aspartic acid, suggesting a simple transformation of the α-acid of the latter.

2. Results and discussion

Our first attempt at synthesizing this molecule consisted in acylating a glycine equivalent with a suitably activated aspartic acid derivative. As depicted in Scheme 2, this synthetic pathway started with commercially available *N*-Cbz aspartic acid α-benzyl ester (*Z*-Asp-OBzl) (**1**). To effect the C-acylation of a glycine-derived enolate, the free side-chain carboxylic acid was first activated with carbonyldiimidazole, but better results were obtained when using an acid chloride. A smooth acylation of the enolate of ethyl *N*-diphenylmethylene glycinate was obtained. The resulting α-imino-β-ketoester was subsequently hydrolysed to yield the unstable hydrochloride **2**. Unfortunately, this aminoketoester did not lead to the expected pyrazine, but underwent a spontaneous cyclisation to afford lactam **3** in 85% overall yield, predominantly observed as its enol tautomer.

Presumably, this result may be explained by the low reactivity of the ketone, due to its propensity for enolization. This low reactivity accounts for an easier intramolecular lactamisation, rather than the desired intermolecular cyclic diimine formation.

This result pointed out the need to lower the reactivity of the α-acid. We initially believed that a reduction of this acid moiety would afford an easy-to-handle alcohol but spontaneous lactonisation of the latter prompted us to introduce the alkyl chain in the first steps of the synthesis.

As shown in Scheme 3, reduction of the free α-acid of commercially available *Z*-Asp(O*t*-Bu)-OH with sodium borohydride after chloroformate activation[3] afforded the alcohol **4**. The optical purity of this alcohol was checked by HPLC on chiral stationary phase and no racemisation was noticed. Mesylation of the latter was successful but further attempt at reacting it with an homocuprate

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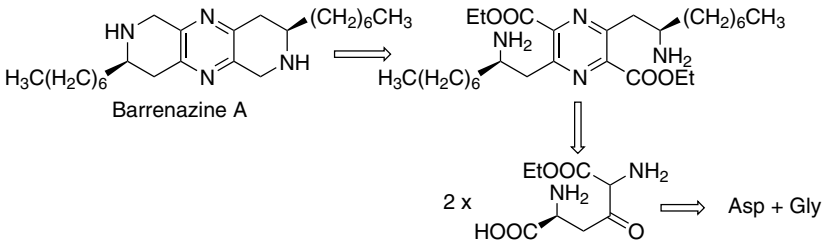
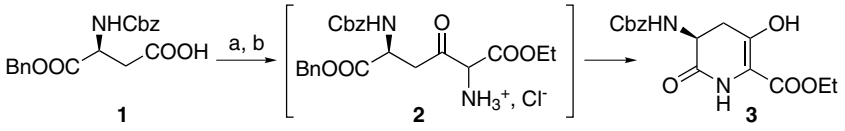
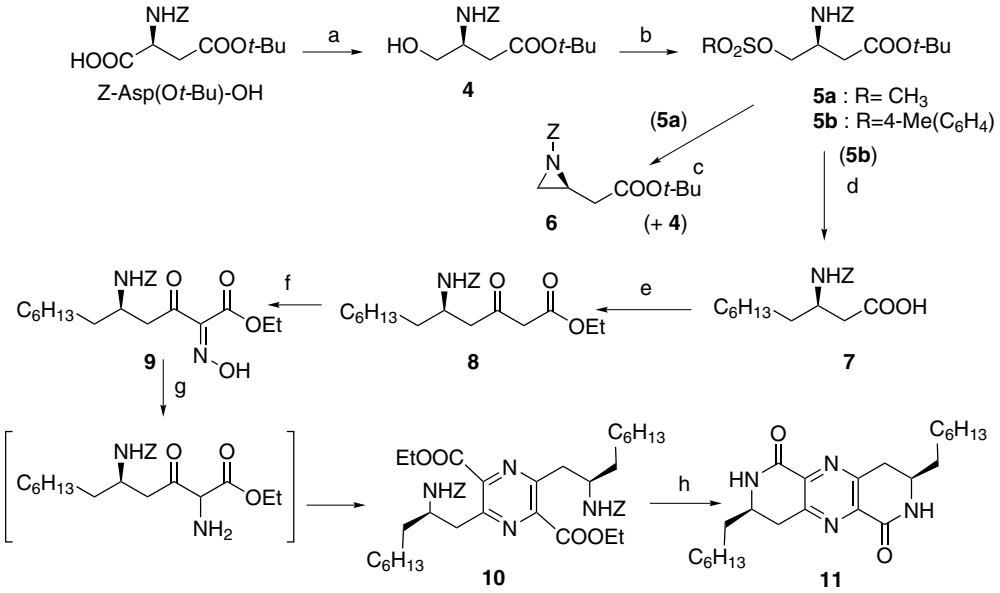


Scheme 1. Retrosynthetic analysis of barrenazine A.



Scheme 2. Reagents and conditions: (a) $(COCl)_2$, cat DMF; (b) $Ph_2C{=}NCH_2COOEt$, *t*-BuOK, THF, −78 to 0 °C, then H_3O^+.



Scheme 3. Reagents and conditions: (a) *N*-methyl morpholine, isobutyl chloroformate, −15 °C, 1 min then aq $NaBH_4$, 88%; (b) RSO_2Cl, Et_3N, cat DMAP, CH_2Cl_2, 0 °C, 54% (**5a**), 91% (**5b**); (c) (*n*-Hex)$CuCNLi_2$, THF, −40 °C, 26% (6); (d) (*n*-Hex)$_2CuLi$, Et_2O, −30 °C, 70% then TFA, CH_2Cl_2, rt, 100%; (e) Meldrum's acid, DCC, DMAP, CH_2Cl_2, rt, then EtOH, reflux, 83%; (f) $NaNO_2$, AcOH, rt, 98%; (g) Zn, AcOH, rt then Et_3N, CH_2Cl_2, air, rt; (h) H_2, Pd/C, AcOH then toluene, reflux, 90%.

led to recovery of the starting alcohol, whereas the cyanocuprate gave a mixture of alcohol **4** and aziridine **6**. The necessary modulation of the leaving group reactivity was obtained by replacing the mesylate with a tosylate. Tosylation of the alcohol proceeded smoothly, leading to **5b** in 91% yield. Introduction of the alkyl group was achieved via treatment with lithium dihexylcuprate and subsequent TFA-mediated deprotection, affording β-aminoacid **7**.[4] Interestingly, this aminoacid was already found in another tunicate, and is a constituent of the peptides Minalemines A and D.[5] Further formation of the pyrazine ring required the obtention of an aminoketoester precursor. First experiments were carried out by acylating diphenyliminoglycine ethyl ester, but with this substrate the reaction was sluggish and the yields were not reproducible. For these reasons we decided to first prepare the β-keto ester before the incorporation of the amino group.

Following this strategy, the acid was converted to the β-ketoester **8** by acylation of Meldrum's acid[6] and refluxing in ethanol. Introduction of the amino group was carried out in a two-step electrophilic amination procedure.[7] Treatment of the β-ketoester with sodium nitrite in acetic acid gave oxime **9** in a nearly quantitative yield, as a mixture of (*E*) and (*Z*) isomers. Further reduction with zinc in acetic acid converted the oxime to the corresponding α-amino-β-ketoester which was not isolated but underwent spontaneous dimerisation followed by air-induced aromatization, to provide pyrazine **10**. The last step was achieved by simultaneous formation of both lactam rings. In this step, amine

deprotection by means of classical hydrogenolysis was followed by rapid intramolecular amidification of ethyl esters.

Compound **11** was finally obtained in 29% yield over eight steps. Unfortunately, attempts at reducing the amide bonds were rendered difficult due to competitive reduction of the pyrazine ring. This was observed with hydrides such as $NaBH_4$ or BH_3, as well as with Raney-nickel desulfurisation of the corresponding thioamide.

3. Conclusion

This concise synthesis of an analogue of the natural enantiomer of barrenazine A was achieved in eight steps from suitably protected aspartic acid. Our retrosynthetic analysis pointed out the assembly of a pair of Asp and Gly, linked together with a carbon–carbon bond and was validated by the easy formation of the pyrazine ring. The natural alkaloid or some of its derivatives may be accessible from diamide **11**.

4. Experimental

4.1. General

Melting points were determined on a Kofler hot-stage apparatus. ^{1}H spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz. IR spectra were obtained from potassium bromide pellets. Anhydrous THF was distilled from sodium/benzophenone. Unless otherwise stated, column chromatographies were carried out through silica gel (230–400 mesh)

4.2. Procedures and data

4.2.1. (5*S*)-5-(Benzyloxycarbonylamino)-3-hydroxy-6-oxo-1,4,5,6-tetrahydropyridine-2-carboxylic acid, ethyl ester (3). A solution of *N*-benzyloxycarbonyl-aspartic acid α-benzyl ester **1** (1 g, 2.80 mmol) and DMF (100 μL) in 50 mL of dichloromethane was cooled to 0 °C and treated with oxalyl chloride (0.53 mL, 4.19 mmol). The solution was stirred for 90 min at rt. The solvent was removed in vacuo and the crude acid chloride was dried under vacuum and used without further purification. A solution of potassium *tert*-butoxide (628 mg, 5.60 mmol) in 50 mL anhydrous THF was cooled to −78 °C under N_2, and *N*-(diphenylmethylene)glycine methyl ester (1.50 g, 5.60 mmol) in 5 mL THF was added. After 30 min, this orange solution was added via cannula to a vigorously stirred solution of the amino acid chloride in 50 mL dry THF at −78 °C. The mixture was stirred for 1 h, allowing the temperature to reach 0 °C. 50 mL of 3 M HCl were added and stirring was kept for 1 h at rt. THF was evaporated and the resultant aqueous layer washed with ether, concentrated in vacuo, taken-up in water and lyophilised. Methanol (20 mL) was added to the residue and precipitated KCl was removed by filtration. Following methanol evaporation, the crude product was purified by column chromatography ($CHCl_3$–MeOH–AcOH, 9:1:0.5) giving **3** (795 mg, 85%) as a yellow solid; mp 155–156 °C. ^{1}H NMR ($CDCl_3$): δ 10.60 (br s, 1H), 7.34 (m, 5H), 5.86 (s, 1H), 5.11 (s, 2H), 4.32 (m, 3H), 3.21 (dd, $J = 16.7$, 6.6 Hz, 1H), 2.65 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 165.8, 164.8, 157.5, 156.1, 136.1, 128.6, 104.3, 67.2, 62.1, 48.9, 32.4, 14.2; IR: 3311, 1659, 1529, 1239, 1073, 782, 746, 694 cm^{-1}. Anal. Calcd for $C_{16}H_{18}N_2O_6$ (334.32): C, 57.48; H, 5.43; N, 8.38. Found: C, 57.32; H, 5.19; N, 8.14.

4.2.2. 3-(*S*)-3-Benzyloxycarbonylamino-4-hydroxy-1-butanoic acid, *t*-butyl ester (4). To a solution of *Z*-Asp-(O*t*-Bu)-OH (2 g, 6.20 mmol) in 50 mL 1,2-dimethoxyethane, was added *N*-methylmorpholine (0.47 mL, 6.51 mmol). The solution was stirred for 10 min at rt and cooled to −15 °C. Isobutyl chloroformate (0.65 mL, 6.51 mmol) was added dropwise. After stirring for 30 s at this temperature, *N*-methylmorpholine hydrochloride was removed by filtration through a short pad of celite, washed with DME and the filtrate transferred to a large flask chilled in an ice-salt bath. A solution of $NaBH_4$ (704 mg, 18.6 mmol) in 5 mL water was added at once, producing a vigorous gas evolution. After stirring for 1 h, 50 mL water was added and the alcohol extracted with ethyl acetate. The crude product was purified by column chromatography (petroleum ether–AcOEt, 1:1), yielding **4** (1.68 g, 88%), as a yellow liquid; $[\alpha]^{20}$ −19.4 (*c* 1.1, $CHCl_3$) (lit.[8]) $[\alpha]^{20}$ −19.6, (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.33 (m, 5H), 5.60 (d, $J = 6.2$ Hz, 1H), 5.10 (s, 2H), 4.30 (m, 1H), 3.67 (d, $J = 4.5$ Hz, 1H), 2.53 (d, $J = 6$ Hz, 2H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 171.2, 156.4, 136.4, 128.6, 81.5, 66.9, 64.4, 50.4, 37.4, 28.1; IR: 3351, 2978, 1714, 1537, 1368, 1256, 1157, 1061, 698 cm^{-1}. Anal. Calcd for $C_{16}H_{23}NO_5$ (309.36): C, 62.12; H, 7.49; N, 4.53. Found: C, 62.08; H, 7.59; N, 4.49.

4.2.3. 3-(*S*)-3-(Benzyloxycarbonylamino)-*p*-toluene sulfonyloxy-butanoic acid *t*-butyl ester (5b). To a solution of compound **3** (1.3 g, 4.20 mmol), triethylamine (0.89 mL, 6.30 mmol) and dimethylaminopyridine (51.3 mg, 0.42 mmol) in 60 mL CH_2Cl_2 under N_2 at 0 °C was added a solution of tosyl chloride (1.20 g, 6.30 mmol) in 5 mL CH_2Cl_2. The reaction medium was stirred for 12 h at 0 °C and poured into ice-water. After extractive work-up with ether, the crude product was purified by column chromatography (heptane–ethyl acetate, 1:1). Compound **5b** crystallised upon trituration in petroleum ether, as a white solid (1.77 g, 91%), mp 81–83 °C. $[\alpha]^{20}$ −10.2 (*c* 1.1, CH_2Cl_2), lit.[4] $[\alpha]^{20}$ −10.2 (*c* 3.1, acetone). ^{1}H NMR ($CDCl_3$): δ 7.77 (d, $J = 8.1$ Hz, 2H), 7.34 (m, 7H), 5.35 (d, $J = 8.6$ Hz, 1H), 5.05 (s, 2H), 4.22 (m, 1H), 4.11 (d, $J = 4.3$ Hz, 2H), 2.53 (d, $J = 5.9$ Hz, 2H), 2.49 (s, 3H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 169.9, 155.5, 145.3, 136.3, 136.3, 128.4, 82.1, 70.2, 67.1, 47.1, 36.3, 28.1, 21.8; IR : 3369, 2971, 1658, 1524, 1023, 855, 698 cm^{-1}. Anal. Calcd for $C_{23}H_{29}NO_7S$ (463.54): C, 59.59; H, 6.31; N, 3.02. Found: C, 60.14; H, 6.41; N, 3.01.

4.2.4. 3-(*R*)-3-Benzyloxycarbonylamino-decanoic acid (7). A solution of 2.3 M *n*-hexyllithium in hexane (19.7 mL, 45.3 mmol) was added dropwise at −20 °C

over 20 min to a suspension of CuI (4.31 g, 22.6 mmol) in dry ether under N_2, turning from a yellow suspension to a clear brown solution. After stirring for 25 min at −20 °C, then cooling down to −30 °C, a solution of tosylate **5b** (3.5 g, 7.55 mmol) in 15 mL dry ether was added over 20 min. The mixture was stirred at −30 °C for 4.5 h and treated with 50 mL satd NH_4Cl and 10 mL concd NH_3. The brown organic layer was diluted with 100 mL ether and 20 mL AcOEt, and washed with brine (3 × 25 mL). After drying and evaporation, the crude product was taken-up in 15 mL dichloromethane and trifluoroacetic acid (2 mL, 27 mmol) was added at rt. After 5 h stirring, the solution was evaporated and the residue was crystallised (petroleum ether–ether, 1:10) to yield **7** (1.70 g, 70%), as a white solid, mp 107–109 °C; $[\alpha]^{20}$ +11.3 (*c* 1.67, CH_2Cl_2), lit.[5] +10.0 (*c* 0.48, $CHCl_3$) ^{1}H NMR ($CDCl_3$): δ 11.16 (m, 1H), 7.34 (m, 5H,), 5.25 (d, $J = 8.8$ Hz, 1H), 5.10 (s, 2H), 3.96 (m, 1H), 2.60 (m, 2H), 1.53 (m, 2H), 1.25 (m, 10H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 177.3; 156.1; 136.4; 128.2; 66.9; 48.0; 38.9–22.7; 14.2; IR: 3331, 1952, 2923, 2853, 1692, 1537, 1258, 1064, 732, 695 cm^{-1}. Anal. Calcd for $C_{18}H_{27}NO_4$ (321.41): C, 67.26; H, 8.47; N, 4.36. Found: C, 67.11; H, 8.45; N, 4.39.

4.2.5. Ethyl 5-(*R*)-5-(benzyloxycarbonylamino)-3-oxododecanoate (8). To a solution of compound **7** (3.3g, 10.2 mmol), Meldrum's acid (1.62 g, 11.3 mmol) and dimethylaminopyridine (0.375 g, 3.1 mmol) in 50 mL CH_2Cl_2 was added *N*,*N*-dicyclohexylcarbodiimide (2.32 g, 11.3 mmol). The solution was stirred for 12 h at rt. *N*,*N*-dicyclohexylurea was filtered off and washed with dichloromethane. The filtrate was washed with 5% HCl (25 mL), brine (30 mL), dried and concentrated. The residue was refluxed in 100 mL absolute ethanol for 5 h. Following ethanol evaporation, the crude product was purified by column chromatography (petroleum ether–AcOEt, 7:3), providing **8** (3.33 g, 83%) as a white solid, mp 83–85 °C. $[\alpha]^{20}$ +10.5 (*c* 1.33, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 7.36 (m, 5H), 5.09 (m, 3H), 4.21 (q, 2H), 3.96 (m, 1H), 3.46 (d, $J = 6$ Hz, 2H), 2.82 (m, 2H),1.53 (m, 2H), 1.28 (m, 13H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 201.9, 167.1, 155.9, 136.2, 128.2, 66.8, 61.6, 49.9, 48.1, 47.2, 34.7–22.7, 14.2; IR: 3316, 2959, 2922, 2854, 1736, 1712, 1681, 1542, 1269 cm^{-1}. Anal. Calcd for $C_{22}H_{33}NO_5$ (391.50): C, 67.49; H, 8.50; N, 3.58. Found: C, 67.24; H, 8.67; N, 3.87.

4.2.6. Ethyl 5(*R*)-2-(hydroxyimino)-5-(benzyloxy carbonylamino)-3-oxododecanoate (9). To a solution of compound **8** (500 mg, 1.27 mmol) in 10 mL acetic acid was added dropwise an ice-cold solution of sodium nitrite (0.45 g, 6.35 mmol) in 3 mL water. The mixture was stirred for 12 h, allowing the temperature to reach rt. Water (10 mL) was added. Extractive work-up with ether afforded **9** as a colourless liquid (523 mg, 98%). ^{1}H NMR ($CDCl_3$): δ 11.6(m, 1H), 7.34 (m, 5H), 5.49 (d, $J = 9.6$ Hz, 1H), 5.05 (m, 2H), 4.38 (q, 2H), 3.96 (m, 1H), 3.16 (m, 2H),1.61 (m, 2H), 1.34 (m, 13H), 0.87 (s, 3H), ^{13}C NMR ($CDCl_3$): δ 194.6, 162.1, 157.1, 136.4, 136.3, 128.5, 67.6, 62.6, 48.1, 41.9, 34.3, 23.0, 14.5; IR: 3375, 2928, 2856, 1693, 1530, 1455, 1259, 1026 cm^{-1}. MS (IC): *m*/*z* (%) = 439 (MNH_4^+); 421 (MH^+).

4.2.7. Diethyl 3(*R*),6(*R*)-3,6-di(benzyloxycarbonyl amino)-pyrazine-2,5-dicarboxylate (10). To a solution of compound **9** (600 mg, 1.47 mmol) in 10 mL acetic acid was added zinc dust (965 mg, 14.7 mmol) in small portions. The reaction mixture was stirred for 12 h at rt, then filtered through a pad of celite, and the solid washed with CH_2Cl_2. The solvents were evaporated, and the residue dissolved in 20 mL dichloromethane. To this solution was added triethylamine (0.62 mL, 4.44 mmol) and the mixture was stirred for 1 h at rt. Additional water (10 mL) was added, and the solution extracted with dichloromethane (3 × 50 mL). The organic layer was washed with brine (30 mL), dried over anhydrous $MgSO_4$ and the solvent evaporated. The crude product was purified by column chromatography (petroleum ether–AcOEt, 7:3), giving **10** (400 mg, 70%), as a white solid, mp 89–91 °C. $[\alpha]^{20}$ −12.3 (*c* 1.54, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 7.21 (m, 5H), 5.56 (d, $J = 8.5$ Hz, 1H), 4.92 (m, 2H), 4.32 (q, 2H), 4.02 (m, 1H), 3.25 (m, 2H),1.47 (m, 2H), 1.25 (m, 13H), 0.79 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 165.0, 156.0, 152.0, 152.0, 136.9, 128.1, 66.5, 62.6, 51.4, 38.7–22.7, 14.2; IR: 3312, 2926, 2854, 1728, 1687, 1541, 1259, 1127, 697 cm^{-1}. Anal. Calcd for $C_{44}H_{62}N_4O_8$ (774.46): C, 68.19; H, 8.06; N, 7.23. Found: C, 68.25; H, 8.07; N, 7.39.

4.2.8. (3*R*,8*R*)-3,8-Diheptyl-3,4,8,9-tetrahydrodipyrido [4,3-*b*:4′,3′-*e*]pyrazine-1,6(2*H*,7*H*)-dione (11). To a solution of compound **10** (200 mg, 0.26 mmol) in 10 mL acetic acid was added 5% Pd/C (55 mg, 0.026 mmol). The mixture was stirred for 1 h at rt under a hydrogen atmosphere and filtered. The precipitate was washed with ethanol, and the solvents evaporated. The solid was dissolved in toluene (15 mL), Et_3N (0.08 mL, 0.52 mmol) was added and the solution was refluxed for 2 h. After cooling, the solution was filtered to give **11** (48 mg, 90%) as a yellow solid. mp >250 °C. $[\alpha]^{20}$ −50.8 (*c* 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 6.54 (s, 1H), 3.84 (m, 1H), 3.50 (dd, $J = 16.6$ and 4.8 Hz, 1H), 3.19 (dd, $J = 16.6$ and 4.8 Hz, 1H), 1.68 (m, 4H), 1.20 (m, 10H), 0.87 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 162.9, 153.6, 142.8, 50.4, 36.1–22.8, 14.2; IR: 3195, 3087, 2957, 2923, 2853, 1693, 1471, 1346, 1192, 807 cm^{-1}. Anal. Calcd for $C_{24}H_{38}N_4O_2$ (414.30): C, 69.53; H, 9.24; N, 13.51. Found: C, 69.47; H, 9.16; N, 13.44.

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